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LAW OFFICE OF MICHAEL A. SANZO, LLC
15400 CALHOUN DR.
SUITE 125
ROCKVILLE, MD 20855

EXAMINER	
STEADMAN, DAVID J	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/733,776	RIEPING, MECHTHILD	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 38-57 are pending in the application.

[2] Applicant's amendment to the claims, filed on 2/13/08, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims. Claims 11, 14-15, 19-20, 22-23, 25, and 28-34 have been canceled and claims 38-57 have been newly added relative to claim set filed on 4/13/07.

[3] Applicant's arguments filed on 2/13/08 in response to the Office action filed on 10/24/07 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[4] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Objections

[5] Applicant is advised that should claim 53 be found allowable, claim 54 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112, Second Paragraph

[6] Claims 55-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 55 (claims 56-57 dependent therefrom) is indefinite in the recitation of "determining the amount recovered" in step b) because it is unclear as to what the amount of is determined – the L-amino acid or some other component? It is suggested that applicant clarify the meaning of the claim by, *e.g.*, replacing the noted phrase with "determining the amount of said L-amino acid recovered".

Claim Rejections - 35 USC § 112, First Paragraph

[7] Claims 38-39, 41-50, and 53-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to a process for producing an L-amino acid as recited in the claims using a modified *E. coli*, wherein the production of the recited L-amino acid is increased. For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings,

or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of the recited genus of L-amino acids that are increased relative to an unmodified *E. coli*, *i.e.*, L-threonine (Example 4 at pp. 25-26). Other than increasing L-threonine production, the specification fails to describe any other L-amino acids whose production is increased using the recited modified *E. coli*. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus," it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." In the instant case, applicant acknowledges that *yjgF* mutations as encompassed by the claims "are suggested [by Enos-Berlage] to block, not promote, bacterial amino acid production" (instant remarks at p. 6). As such, a skilled artisan would recognize that the disclosure of increased L-threonine production fails to represent increased production of other amino acids as encompassed by the claims.

Given the lack of description of a representative number of polypeptides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[8] Claims 38-39, 41-50, and 53-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for increased production of L-threonine, does not reasonably provide enablement for a process for increased production of L-amino acids other than L-threonine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation is required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). MPEP 2164.04 states, "[w]hile the analysis and conclusion of a lack of enablement are based on the factors discussed

in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection" and that "[t]he language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims." Accordingly, the Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: The claims encompass methods of increased production of L-amino acids other than L-threonine. The enablement provided by the specification is not commensurate in scope with the claims with regard to the scope of L-amino acids whose production is increased by practicing the claimed methods. In this case, the specification is enabling only for a process for increasing production of L-threonine.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: According to applicant, *yjgF* mutations as encompassed by the claims "are suggested [by Enos-Berlage] to block, not promote, bacterial amino acid production" (instant remarks at p. 6). As such, a skilled artisan would recognize it is highly unpredictable as to whether or not inactivating mutations to *yjgf* would result in an increased production of *any* L-amino acid as encompassed by the claims.

The amount of direction provided by the inventor and The existence of working examples: In this case, the specification discloses only a single working example of increased production of an L-amino acid, *i.e.,* increased production of L-threonine (pp.

25-26, Example 4). The specification fails to disclose any guidance or provide any expectation of increased production of L-amino acids other than L-threonine.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While L-amino acid production methods were known in the prior art at the time of the invention, since the prior art acknowledged that "*yjgF* mutations are suggested to block, not promote, bacterial amino acid production" (instant remarks at p. 6), a skilled artisan would recognize that there is no way to determine – if any – the amount of additional experimentation that is required to achieve increased production of L-amino acids other than L-threonine.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required, undue experimentation is necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

[9] Claim(s) 38-47 are rejected under 35 U.S.C. 102(e) as being anticipated by Kruse et al. (US Patent Application Publication 2007/0092950; "Kruse1"). The teachings of Kruse1 were first disclosed in provisional application 60/494,566, filed on 8/13/03.

The applied reference has a common assignee or inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e)

might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. Also, the instant rejection based on the reference of Kruse1 may also be overcome by the filing of an English-language translation of the foreign priority document, DE 10303571.0.

The claims are drawn to a method for the production of an L-amino acid by culturing an *Escherichia* bacterium and recovering or isolating the L-amino acid; wherein the yjgF open reading frame of the bacterium has been modified according to the claims, wherein the modification results in an increased production of L-amino acid.

The reference of Kruse1 teaches a method for producing L-threonine using an *E. coli* including a mutation to attenuate the *E. coli yjgF* gene (claims 40 and 60; pp. 7-8, paragraph 100; p. 10, paragraph 137 of Kruse1), wherein attenuation is a result of mutation including transition, transversion, insertion, and deletion mutagenesis (p. 10, paragraphs 131-132), discusses using batch, fed batch, and repeated fed batch culturing methods in the production method (p. 1, paragraph 5 of Kruse1), collecting the L-amino acid (p. 4, paragraph 45 of Kruse1), and analyzing the L-threonine (p. 4, paragraph 52). This anticipates claims 38-47 as written.

[10] Claim(s) 38-47 are rejected under 35 U.S.C. 102(e) as being anticipated by Kruse et al. (WO 2005/014841; "Kruse2"). The teachings of Kruse2 were first disclosed in provisional application 60/491,982, filed on 8/4/03.

The applied reference has a common assignee or inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. Also, the instant rejection based on the reference of Kruse1 may also be overcome by the filing of an English-language translation of the foreign priority document, DE 10303571.0.

The claims are drawn to a method for the production of an L-amino acid by culturing an *Escherichia* bacterium and recovering or isolating the L-amino acid; wherein the yjgF open reading frame of the bacterium has been modified according to the claims, wherein the modification results in an increased production of L-amino acid.

The reference of Kruse2 teaches a method for producing L-threonine using an *E. coli* including a mutation to attenuate the *E. coli yjgF* gene (claim 39; pp. 29-30, bridging paragraph), wherein attenuation is a result of mutation including transition, transversion, insertion, and deletion mutagenesis (p. 37, lines 19+), discusses using batch, fed batch, and repeated fed batch culturing methods in the production method (pp. 1 and 9-12), collecting the L-amino acid, and analyzing the L-threonine (pp. 16-17). This anticipates claims 38-47 as written.

Claim Rejections - 35 USC § 103

[11] Claim(s) 38-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Volz (*Protein Sci* 8:2428-2437, 1999; cited in the IDS filed on 11/18/2004) in view of Enos-Berlage et al. (*J. Bacteriol* 180:6519-6528, 1998; cited in the IDS filed on 11/18/2004; "Enos-Berlage"), Verkhovskaya et al. (*Microbiol.* 147:3005-3013, 2001; "Verkhovskaya"), and Promega Technical Bulletin No. 117 (September, 2002). It is noted that claims 46-47 have been included in the instant rejection as batch culturing, fed batch culturing, and repeated fed batch culturing are recognized in the prior art as being alternative methods of culturing a microorganism as acknowledged by applicant at specification p. 20, lines 8-17.

The claims are drawn to a method for the production of an L-amino acid by culturing an *Escherichia* bacterium and recovering or isolating the L-amino acid; wherein the yjgF open reading frame of the bacterium has been modified according to the claims, wherein the modification results in an increased production of L-amino acid.

The reference of Volz teaches an attempt to ascertain the function of an *Escherichia coli yjgF* gene product (Yjgf) by analysis of its crystal structure (p. 2428, abstract) and that "[a]lthough the sequence-to-structure-to-function approach was not successful in this test case, the results suggest a variety of experiments that should complete the goal…More general experiments include determination of the phenotype of an organism (*E. coli, S. cerevisiae, or Caenorhabditis elegans*) after deletions of all YjgF paralogs. Preliminary results toward this approach with *S. typhimurium* have already been reported (Enos-Berlage et al., 1998)" (p. 2435, column 1, top). Volz teaches the sequence of *E. coli* YjgF (p. 2429). Although suggested by Volz, this

reference does not teach an *E. coli* with a deleted *yjgF* gene, nor does the reference teach culturing of such *E. coli* or isolating an L-amino acid.

The reference of Enos-Berlage, which is cited by Volz, teaches a method of phenotyptic characterization of the *S. typhimurium yjgF* gene product using a ygjF-negative mutant created by inactivation of the *S. typhimurium yjgF* gene (p. 6519, abstract and 6520, column 2, top) and further teaches the sequence of *E. coli* YjgF polypeptide (p. 6523, Figure 3).

At the time of the invention, methods for gene inactivation in an *E. coli* bacterium were well-known in the prior art. For example, the reference of Verkhovskaya teaches a method for deleting a gene in *E. coli* by gene knockout, which method encompasses verification of genotype by PCR (see *Interruption of* yjcE *(GRN11 strain)* at p. 3006, bridging columns 1-2), wherein the reference of Verkhovskaya teaches the genomic DNA was prepared by Wizard® DNA purification system. According to the Wizard® instructions in Promega Technical Bulletin No. 117, the method includes preparing an overnight bacterial culture (*e.g.,* p. 6, middle), centrifuging the culture to separate the cells from the liquid medium (*e.g.,* p. 3, step III.A.1), lysing the cells and centrifuging to remove cell debris (*e.g.,* p. 3, step III.A.2.-5.), and removing the lysate from the cell debris (*e.g.,* p. 4, step IV.A.2.).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Volz, Enos-Berlage, Verkhovskaya, and Promega Technical Bulletin No. 117, to make an *E. coli* with deletion of a *yjgF* gene, culture the resulting mutant *E. coli,* and obtain a cell-free lysate thereof. One would have been motivated to

do this because of the express suggestion of Volz as noted above, particularly as Volz is concerned with determining the function of an *E. coli* YjgF protein. One would have a reasonable expectation of success for making an *E. coli* with deletion of the *yjgF* gene, culture the resulting mutant *E. coli,* and prepare a cell-free lysate thereof because of the results of Enos-Berlage, Verkhovskaya, and Promega Technical Bulletin No. 117. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to make an *E. coli* with deletion of a *yjgF* gene, culture the resulting mutant *E. coli,* and obtain a cell-free lysate thereof, which method would have necessarily resulted in practicing the methods of claims 38-57.

The following comments are provided in order to clarify the instant rejection. While the combination of cited references does not *expressly* teach recovery or isolation of an L-amino acid from an *E. coli* with deletion of the *yjgF* gene or the culture medium thereof, by isolating a cell free lysate of *E. coli* with deletion of the *yjgF* gene (*e.g.,* p. 4, step IV.A.2. of Promega Technical Bulletin No. 117) or isolating the liquid medium from the *E. coli* cells with deletion of the yjgF gene (*e.g.,* p. 3, step III.A.1 of Promega Technical Bulletin No. 117), one would necessarily recover or isolate the L-amino acid in accordance with the claims, particularly as the specification (p. 4, lines 6-9) discloses, "isolation of the desired L-amino acid, constituents of the fermentation broth and/or the biomass in its entirety or portions (>0 to 100 %) thereof optionally remaining in the product." ("[T]he specification 'is always highly relevant to the claim construction analysis. Usually it is dispositive; it is the best single guide to the meaning of a disputed term.'" *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315, 75 USPQ2d 1321, 1327 (Fed. Cir.

2005)). Also, while the combination of references fails to *expressly* teach the production of an L-amino acid, or the amino acid(s) recited in claims 39-40, 50-54, and 57, in accordance with the evidence provided in the specification, this would be a necessary feature of culturing an *E. coli* with deletion of the *yjgF* gene as suggested by Volz.

[12] In the event applicant provides a line of reasoning and/or evidence that batch, fed batch, and repeated fed batch culturing methods are not art-recognized equivalents, claim(s) 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Volz in view of Enos-Berlage, Verkhovskaya, and Promega Technical Bulletin as applied to claims 38-45 and 48-57 above and further in view of Lee (*Trends Biotechnol.* 14:98-105, 1996). Claims 46-47 limit the culturing method to fed batch culturing and repeated fed batch culturing. The examiner has interpreted the term "repeated fed batch" to include a fed batch process that is conducted more than once.

The relevant teachings of the references of Volz, Enos-Berlage, Verkhovskaya, and Promega Technical Bulletin are set forth above. The combined references do not expressly teach using fed batch culturing and repeated fed batch culturing for recombinant protein production.

Lee teaches fed batch culturing of *E. coli* for high cell density culturing, which has several advantages, including reduced culture volume, reduced wastewater, and reduced investment in equipment (p. 98, column 2).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Volz, Enos-Berlage, Verkhovskaya, Promega Technical

Bulletin No. 117, and Lee to make an *E. coli* with deletion of a *yjgF* gene, fed batch or repeated fed batch culture the resulting mutant *E. coli,* and obtain a cell-free lysate thereof. One would have been motivated to do this because of the express suggestion of Volz as noted above, particularly as Volz is concerned with determining the function of an *E. coli* YjgF protein and because fed batch or repeated fed batch culture has the advantages as noted by Lee. One would have a reasonable expectation of success for making an *E. coli* with deletion of the *yjgF* gene, fed batch or repeated fed batch culturing of the resulting mutant *E. coli,* and prepare a cell-free lysate thereof because of the results of Enos-Berlage, Verkhovskaya, Promega Technical Bulletin No. 117, and Lee. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to make an *E. coli* with deletion of a *yjgF* gene, fed batch or repeated fed batch culture the resulting mutant *E. coli,* and obtain a cell-free lysate thereof, which method would have necessarily resulted in practicing the methods of claims 47-48.

RESPONSE TO ARGUMENT: Beginning at p. 6 of the instant remarks, applicant provides comments concerning the content of the cited references as follows: 1) Volz is "concerned with analysis of the normal [*yjgf*] gene product, not mutated forms of the product" and "never suggests that a loss of *yjgF* gene function leads to increased bacterial amino acid production or otherwise suggests that bacteria with mutations in *yjgF* might be cultured and used to make amino acids"; 2) Enos-Berlage "does not suggest that bacteria containing a mutated *yjgF* gene should be used for fermentatively producing amino acids and, as discussed further below, there are statements in the

reference that actually appear to suggest that bacteria containing such mutations should *not* be used in the production of amino acids, *i.e.,* that teach away from the claimed invention"; 3) the disclosed technique of Verhovskaya and Promega Bulletin "would not *necessarily* be used…one wanting to find the function *of yjgF* could use a different mutagenesis procedure or could try increasing, rather than decreasing, the activity of the gene and see what phenotypic consequences this had"; 4) Kruse "does not suggest that all assay conditions are suitable for amino acid production…the switching from LB medium to a defined medium suggests otherwise"; and 5) the examiner has not met the initial burden for establishing a *prima facie* case of obviousness.

Regarding comment 1), Volz clearly suggests deletion of the *E. coli ygjF* gene, which is undisputed by applicant and as noted in the prior Office action, and although the reference of Volz fails to expressly teach increased amino acid production or the use of *E. coli* with a deleted *ygjF* gene for amino acid production, it is not only the express teachings that may be relied upon, but instead, as acknowledged by MPEP 2112, the implicit and inherent teachings of the combination of the cited prior art references may be relied upon in making an obviousness rejection.

Regarding comment 2), as noted above, it is not only the express teachings that may be relied upon, but instead, as acknowledged by MPEP 2112, the implicit and inherent teachings of the combination of the cited prior art references may be relied upon in making an obviousness rejection. Applicant's assertion that the reference teaches away from the claimed invention will be addressed below.

Regarding comment 3), as acknowledged by applicant, the method could have been applied to deleting the *yjgF* gene, *i.e.,* there is no teaching away from using the disclosed method. Although applicant suggests that one desiring to delete the *yjgF* gene alternatively could have used a different mutagenesis procedure, it is noted that this would have been a preferred method since it would have resulted in specific deletion of the *yjgF* gene. In this regard, applicant fails to offer an alternative that would have been preferential to that of the cited reference and would not have resulted in the culturing of the modified bacterium. Also, although applicant suggests that one desiring to delete the *yjgF* gene alternatively could have tried increasing, rather than decreasing, the activity of the gene, the Volz reference specifically suggests deleting the gene.

Regarding comment 4), which addresses a reference used to counter applicant's assertion that *S. typhimurium* culture conditions as disclosed by Enos-Berlage are not conducive to amino acid production, as noted in the prior Office action, according to MPEP 2145, "[t]he arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997)." As noted in the prior Office action, one would have used those conditions suitable for culturing of *E. coli,* not *S. typhimurium,* which is undisputed by applicant. Moreover, that cultured *E. coli* is able to produce L-threonine is evidenced by the reference of Kruse. It is noted that the instant claims do not require any particular culture medium nor does the instant specification appear to disclose that any particular medium is required for L-threonine production. To the contrary, the specification even suggests that such culture medium is art-recognized

by referring to prior art references (p. 20). In the interest of compact prosecution, applicant is advised that if the position that LB medium is not conducive to *E. coli* L-amino acid or L-threonine production, such position may be relied upon by the examiner as a basis for an enablement rejection under 35 U.S.C. 112, first paragraph.

Regarding comment 5), the examiner maintains that the relevant teachings of the combination of cited references expressly, implicitly, or inherently teaches all limitations of the claims, provides motivation for practicing the method, and provides a reasonable expectation of success for the reasons set forth above.

Beginning at p. 8 of the instant remarks, applicant presents factual considerations regarding the rejection: 1) the cited references fail to teach or suggest culturing, lysing, and centrifugation of the lysate; 2) the references fail to teach or suggest that such a method would result in recovering or isolating amino acids; and 3) one should look to the end result of a process to determine if purification or isolation has occurred.

Regarding factual consideration 1), applicant is urged to consider the combination of references rather than considering the references individually. When one considers the *combination* of references, by deleting the *ygjF* gene in *E. coli* as suggested by Volz using the methods of Verhovskaya and Promega Bulletin would have cultured, lysed, centrifuged the lysate and separated the lysate and debris (see paragraph bridging pp. 4-5 of the Office action filed on 10/24/07).

Regarding factual consideration 2),as noted above, it is not only the express teachings that may be relied upon, but instead, as acknowledged by MPEP 2112, the implicit and inherent teachings of the combination of the cited prior art references may be relied upon in making an obviousness rejection.

Regarding factual consideration 3), as noted in the prior Office action, "by isolating a cell free lysate...or isolating the liquid medium from the *E. coli* cells...one would necessarily recover or isolate the L-amino acid. Although applicant does not appear to dispute that such method steps result in recovering or isolating an amino acid, applicant appears to take the position that such steps cannot, by ordinary usage of the term "isolate" or "recover" be encompassed by the claims since the method of the prior art does not stop at the point of isolating a cell free lysate or isolating the liquid medium from the *E. coli* cells. However, such position would appear to go against MPEP 2111.01, which states, "During examination, the claims must be interpreted as broadly as their terms reasonably allow". In this case, the method suggested by the prior art isolates or recovers amino acids as noted above and in accordance with MPEP 2111, the examiner has broadly, but reasonably interpreted the noted steps as being encompassed by the claims.

Beginning at p. 10 of the instant remarks, applicant presents legal considerations regarding the rejection: 1) the cited references fail to teach or suggest a relationship between *yjgF* gene and amino acid production; 2) an inherency rationale cannot be relied upon in an obviousness rejection; 3) there is no indication that the conditions of

Enos-Berlage are conducive to amino acid production; and 4) Enos-Berlage suggests that loss of *ygjF* function should decrease, not increase amino acid production.

Regarding legal considerations 1 and 2), applicant's attention is directed to MPEP 2112, which states (in relevant part), "[t]he express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. 'The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness.'" According to MPEP 2112.II, "There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003)". See also MPEP 2112.02, which states, "Under the principles of inherency, if a prior art device, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art device. When the prior art device is the same as a device described in the specification for carrying out the claimed method, it can be assumed the device will inherently perform the claimed process". Even though the combination of references fails to *expressly* teach a relationship between a *yjgf* mutation and amino acid production, the *implicit* and *inherent* teachings of the prior art must nonetheless be considered in determining whether the claimed method would have been obvious at the time of the invention. In this case, the method as suggested by the prior art would have necessarily resulted production and isolation or recovery of an L-amino acid as encompassed by the claims.

As an aside, it should be noted that the L-amino acid that is isolated or recovered is not required to have been produced by the cultured bacterium. The claims only require culturing the bacterium "under conditions suitable" for L-amino acid production, never requiring the bacterium actually produce an L-amino acid. Thus, it is reasonable to interpret the claims as encompassing recovering or isolating an L-amino acid that is present in the culture medium as a nutrient, not as a product produced by the recited bacterium.

Regarding legal consideration 3), as noted in the prior Office action, one of ordinary skill in the art would not use conditions for culturing *S. typhimurium* for culturing *E. coli.* Instead, one would have used conditions for culturing *E. coli,* which, as acknowledged by the specification at p. 20, were well-known in the art at the time of the invention.

Regarding legal consideration 4), as noted above, MPEP 2112.02 acknowledges that "Under the principles of inherency, if a prior art device, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art device. When the prior art device is the same as a device described in the specification for carrying out the claimed method, it can be assumed the device will inherently perform the claimed process". As such, by practicing the suggested method of the prior art, enhanced amino acid production would have been a necessary result of practicing the prior-art suggested method.

[13] Claim(s) 48-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kruse1 OR Kruse2. The teachings of Kruse1 were first disclosed in provisional application 60/494,566, filed on 8/13/03 and the teachings of Kruse2 were first disclosed in provisional application 60/491,982, filed on 8/4/03.

The applied references have a common inventor and/or assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The claims are drawn to a method for the production of an L-amino acid by culturing an *Escherichia* bacterium and recovering or isolating the L-amino acid; wherein the yjgF open reading frame of the bacterium has been modified according to the claims, wherein the modification results in an increased production of L-amino acid.

The relevant teachings of Kruse1 OR Kruse2 are set forth above. The reference of Kruse1 or Kruse2 does not expressly teach deleting all of the *yjgF* gene (claims 48-54), producing L-homoserine (claims 53-54), or determining the amount of L-amino acid recovered (claims 54-57).

However, practicing the method of Kruse1 or Kruse2 and deleting all of the *yjgF* gene, producing L-homoserine, or determining the amount of L-amino acid recovered would have been obvious to one of ordinary skill in the art at the time of the invention. One would have been motivated to delete all of the *yjgF* gene in the method of Kruse1 or Kruse2 in order to avoid any complication(s) as a result of expressing a truncated version of the *yjgF* gene. One would have been motivated to produce L-homoserine in the method of Kruse1 or Kruse2 because L-homoserine is a biosynthetic precursor of threonine, L-homoserine is an industrially useful amino acid, further because Kruse1 and Kruse2 specifically teach the use of L-homoserine feedback-resistant *E. coli* in practicing the disclosed method. One would have been motivated to determine the amount of L-threonine recovered in order to determine the yield of product. One would have a reasonable expectation of success for practicing the method of Kruse1 or Kruse2 and deleting all of the *yjgF* gene, producing L-homoserine, or determining the amount of L-amino acid recovered because of the results of Kruse1 or Kruse2, respectively. Therefore, claims 48-57, drawn to the method as noted above, would have been obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

[14] Status of the claims:

Claims 38-57 are pending.

Claims 38-57 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656